REMARKS

With the present submission, claims 18 and 33-37 have been amended. As such, claims 18-20 and 33-38 are currently under consideration.

Specifically, claim 18 has been amended to recite "a sense strand" and "an antisense strand," instead of "a first strand" and "a second strand," respectively. Part b) of the previously presented claim 18 has been deleted. In new part b) of claim 18, the term "about" has been removed. In new part c), the enumerated terminal cap moieties, as amended, are recited as alternatives. Semicolons separating certain enumerated terminal cap moieties have been changed to commas to more accurately reflect that alternative relationship. Claim 18, as amended, finds support in the as-filed application at, *inter alia,* Figure 22, and pages 42-47. Claim 18, as amended, is also supported by the priority applications, such as, for example, the U.S. Provisional Application 60/358,580, at, *inter alia,* page 35, lines 1-27.

Claims 33-37 have been amended to remove the references to "the first strand" and "the second strand," replacing them with "the sense strand" and "the antisense strand," respectively. Claim 36 has also been amended so that it ends with a period. These amendments were made solely to insure proper antecedent basis and formality without altering the scope of their corresponding claims.

Amendments to the claims are made without prejudice or disclaimer, and do not constitute amendments to overcome any prior art or other statutory rejections. As explained above, they are fully supported by the specification as filed and thus do not introduce new matter. Additionally, these amendments are not and should not be construed as admissions regarding the patentability of the claimed or canceled subject matter. Applicants reserve the right to pursue the subject matter of the previously presented claims in this or in any other appropriate applications. Accordingly, Applicants respectfully request entry of the proposed amendments.

Priority

Applicants thank the Office for acknowledging and according the pending claims the priority date of February 20, 2002, on which U.S. Provisional Application No. 60/358,580 was filed.

Claim rejections under 35 U.S.C. § 103(a)

Claims 18-20 and 33-38 stand rejected as allegedly being obvious over Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), in view of Matulic-Adamic *et al.* (US 5,998,203), Parrish *et al.* (Molecular Cell, Vol. 6, pages 1077-1087, 2000), and Crooke (US 5,898,031).

At the outset, it is respectfully noted that the instantly claimed invention is drawn to a double stranded nucleic acid molecule, wherein each strand is 18 to 27 nucleotides long with 18 to 23 nucleotides of one strand being base-paired with nucleotides of the other strand, and wherein there is a terminal cap on each end of the sense strand and optionally an additional terminal cap on the 3'-terminal of the antisense strand. Moreover, the caps of the present invention are specifically enumerated. To assist visualization, the molecule can be represented by the formula:

(sense) **5'-Cap A**--------$N_{(18-27)}$-------**Cap B-3'**

(antisense) **3'-(Cap C)** -------$N_{(18-27)}$------5'

wherein the parentheses around "Cap C" indicate Cap C is optional. As such, the claimed molecule is not rendered obvious by the cited prior art because these references alone or in combination does not teach or suggest the claimed construct.

For example, Elbashir does not teach terminal caps at all. The Office alleged that the instant application does not define the term "terminal cap" thus the modified "terminal nucleotides of the siRNA duplexes of Elbashir et al. meet the instant limitation of including a terminal cap." *See* Office Action mailed June 12, 2006, at page 8. Applicants respectfully traverse.

First, the instant specification does in fact define the term "terminal cap," in multiple places, for example, at page 12, lines 21-23 ("In one embodiment, a siNA molecule of the invention comprises a sense region and antisense region, wherein the sense region includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense region. In another embodiment, the terminal cap moiety is an inverted deoxy abasic moiety or any other cap moiety such as those shown in **Figure 22**."); at page 22, lines 14-15 (describing that the cap moiety can be an inverted deoxy abasic moiety, an inverted deoxy thymidine moiety, or a thymidine moiety); page 42, line 8, to page 47, line 33 (describing various base-, sugar-, and

phosphate backbone- modifications, *in addition* to a terminal cap moiety on the ends of the strands); page 73, lines 6-23 (*inter alia*, "the terminal cap moiety comprises an inverted abasic, inverted deoxy abasic, inverted nucleotide moiety, a group shown in **Figure 22**, an alkyl or cycloalkyl group, a heterocycle, or any other group that prevents RNAi activity in which the second sequence serves as a guide sequence or template for RNAi."). Therefore, the terminal cap moieties of the instant claim 1 are present *in addition to* the sugar-, base-, or phosphate backbone- modifications that may exist on the terminal nucleotides. Moreover, in accordance with the present invention, a terminal cap moiety serves to prevent the loading of a capped sequence from the capped end into the RISC complex.

The terminal nucleotides of Elbashir et al. therefore do not comprise terminal cap moieties as contemplated in the present application, despite being chemically modified. The modifications on the terminal residues of the Elbashir molecules would not be equated with the term "terminal caps," as defined in the instant application, by those of ordinary skill in the art.

But even assuming the modifications on the terminal nucleotides were considered caps, a notion to which Applicants strongly traverse, neither Elbashir nor the secondary references, alone or in combination, teach or suggest a molecule having modifications on both ends of the sense strand and optionally on only the 3'-end of the antisense strand. It is respectfully noted that all the terminally-positioned modified nucleotides of Elbashir are positioned on the 3'-overhangs. Therefore, even if Elbashir did teach terminal cap modification, which it certainly did not, it would have taught nothing more than a molecule of the following structure:

(sense) 5'-------$N_{(18-25)}$ ----------**modified overhang**-3'
(antisense) 3'-**modified overhang** -------$N_{(18-25)}$ ---------- 5'

The Elbashir molecule thus clearly does not inform the design of short nucleic acid duplex comprising dual caps on the sense strand and an optional 3'-cap on the antisense strand, as presently claimed.

Matulic-Adamic adds nothing in this respect. Specifically, Matulic-Adamic pertains to a single-stranded ribozymes molecule, which by definition cannot have a sense strand and a separate antisense strand (*i.e.,* is not a double-stranded nucleic acid molecule). As such, it cannot have a cap at the 5' end and 3' end of the sense strand and optionally a cap at the 3' end of the antisense strand.

Parrish does not teach or suggest a molecule having dual caps on the sense strand and an

optional single cap on the 3'-end of the antisense strand, either. In fact, Parrish does not teach chemical modification of short nucleic acid duplexes but rather modification of long (about 742 nts) RNA. None of the terminal caps enumerated in the instant claim 1 ever appeared in Parrish, and there was simply no modification in the four-corners of Parrish that can reasonably be called "a terminal cap" in accordance with the definition of that term in the instant application.

Crooke allegedly teaches "experimentally determining optimal locations and levels of modification of antisense oligonucleotides." *See* Office Action, at page 4. However, there is nothing in Crook to teach or suggest the specific claimed feature that the sense strand having dual terminal caps and the antisense strand having optionally a terminal cap on the 3'-end, or that the terminal cap be one among the enumerated list of terminal caps recited in the instant claim 1. Thus, Elbashir, Matulic-Adamic, Parrish, and Crooke, *alone or in combination,* failed to teach or suggest each and every limitation of the present invention.

It is respectfully noted that the obviousness rejections raised in the instant Office Action and various prior Office Actions are premised upon, or at least mostly premised upon, the fact that the dependent claims are drawn to chemically modified molecules comprising various base, sugar and backbone modifications. *See, e.g.,* Office Action, dated October 30, 2007, at pages 3-9; Office Action, dated June 12, 2006, at pages 7-16. But because instant claim 1 recites the feature of dual terminal caps on the sense strand and an optional single terminal cap at the 3'-end of the antisense strand, and because that feature is, by virtue of the dependency, also present in each of the dependent claims, prior art references that do not render instant claim 1 obvious would not render the dependent claims obvious. As stated above, the cited references, *alone or in combination,* failed to teach or suggest every limitation of instant claim 1. Thus these references cannot be properly coalesced into a ground on which to base a *prima facie* case of obviousness against claim 1 or any claims depending therefrom.

Furthermore, there is nothing in the cited art that would have given the ordinary artisan reason to expect that constructs having the cap structures as presently claimed would induce RNAi. One of ordinary skill in the art could not have reasonably predicted that capping the ends of the strands with chemical moieties in the specific pattern as recited in the present claims would yield constructs having the ability to induce RNAi. As such, the presently claimed molecules cannot be obvious.

Accordingly, Applicants respectfully request the withdrawal of the outstanding

obviousness rejection.

Claim Objections

Claim 36 has been objected to for alleged informalities because it does not end with a period. Claim 36, as amended, ends with a period, thereby obviating the Office's concern.

Claim Rejections – 35 U.S.C. § 112, second paragraph

Claims 18-20 and 33-38 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failure to particularly point out and distinctly claimed the inventive subject matter. *See* Office Action, at page 10. Specifically, claim 18 has been rejected because the limitations "said 3'-end terminal cap moieties" and "said 5'-end cap moieties" allegedly lack antecedent basis. *See id.* Claims 19-20 and 33-38 have been rejected because they depend from claim 18. *See id.*

Without acquiescing to the Office's contentions, Applicants have amended claim 18 to recite "the terminal cap moiety at the 3'-end" and "the terminal cap moiety at the 5'-end," thereby obviating the Office's concerns. As such, Applicants respectfully request withdrawal of these rejections.

Double Patenting

Claims 18-20 and 33-38 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 1, 15-18, 32, 36-40, 42-44 and 46-51 of copending Application No. 10/667,271. *See* Office Action, at page 11. These claims have also been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 15-18, 32, 36-40, 42-44, and 46-51 of copending Application No. 10/669,841. *See* Office Action, at page 12. Furthermore, the Office alleged that an obviousness-type double patenting rejection would be applied in view of claims contained in 10/664,668; 10/576,690, 11/265,730, 10/576,751; 11/684,465; 11/369,108; 10/567,888; 10/923,536; 11/499,633; 11/499,529; 11/499,520; 11/502,893; 10/562,561; 10/825,485; 11/255,139; and 10/921,554. *See* Office Action, at page 13.

Without acquiescing to the Office's contentions, Applicants respectfully submit that they will consider filing one or more terminal disclaimers, if appropriate, when the claims are otherwise in final, allowable form.

Conclusion

For the reasons stated above, Applicants respectfully request withdrawal of the outstanding rejections and objections and early allowance of the pending claims. If the Examiner believes a telephone conference would advance prosecution, she is urged to contact the undersigned at the number below.

Respectfully submitted,

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/Michael S. Greenfield/
Michael S. Greenfield
Registration No. 37,142

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone:312-913-0001
Facsimile: 312-913-0002